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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,980	09/19/2003	Robin L. Davisson	P05473US01	8688

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EXAMINER	
ALONZO, NORMA LYN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,980	DAVISSON, ROBIN L.	
	Examiner	Art Unit	
	Norma C Alonzo	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) 6-12 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-5 and 13-21 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 19 September 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1-21 are pending in the instant application.

2. Applicant's election of Group 1, claims 1-5, 13-16 and 17-21, drawn to a method of screening for compounds useful in treatment or prevention of preeclampsia, in the reply filed on 10/21/04 acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 69 and 10-12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/21/04.

4. Claims 1-5 and 13-21 are under consideration.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 1-5 and 13-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening for compounds useful for the treatment or amelioration of preeclampsia and/or symptoms thereof comprising inducing preeclampsia in a BPH/5 murine animal, does not reasonably provide enablement for a method for screening for compounds useful for the treatment or amelioration of preeclampsia and/or symptoms thereof comprising inducing preeclampsia in any animal with a BPH/5 phenotype. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 , 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses a method for screening for compounds in the treatment or amelioration of preeclampsia comprising inducing preeclampsia in any animal with a BPH/5 phenotype.

The nature of the invention is a method of using any animal exhibiting BPH/5 phenotype or, similarly, any preeclampsia phenotype. As cited in the disclosure, "the term 'BPH/5 mouse' is intended to refer to an inbred subline generated from brother-sister matings of fully inbred BPH/2 mice over many generations, or any other mouse, derived from this line or not, which exhibits symptoms of preeclampsia when the female is impregnated, . . ." (page 11, lines 13-16) Wherein the state of the art of preeclampsia and the BPH/5 phenotype, the condition is verified for existence in other murine models, the art does not teach the BPH/5 phenotype in any animal other than murine. (Douglas BH Perspect Nephrol Hypertens 5:411-419, 1976; Crossey et al. J Clin Invest 110(3): 411-418, 2002; Bohlender et al. J Am Soc Nephrol 11(11) : 2056-2061, 2000) Wherein the claims are directed to a BPH/5 animal or phenotype, a skilled artisan would have to be given specific guidance to make any BPH/5 animal. However, as the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. The variation in expression levels between different cell lines and species may be attributed to host genetic background, the site of chromosomal insertion and absence of specific transcription factors. Cameron (Cameron ER Molecular Biotechnology 7:253-276, 1997) noted, "Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels

or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tigssues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy-number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

Hammer et al. (Hammer RE et al. Cell 63 :1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rat demonstrated the most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the integration of a transgene into alternative species may result in a widely different phenotypic response even in animals of the same species.

Further, the genus of the claimed invention "an animal with a BPH/5 phenotype" is very broad, encompassing not only mammalian species, but amphibians, reptiles, and insects. Wherein the reproductive systems of such phylogenetically distant species are so diverse, specific guidance to make and use a BPH/5 mouse model of preeclampsia does not enable a skilled artisan to make and use a BPH/5 model of preeclampsia of any animal species other than murine. Therefore, without specific guidance from the art or from the instant specification, the making and using of a BPH/5 animal as a model for preeclampsia in a method for screening compounds useful for the treatment or

amelioration of symptoms of preeclampsia in any animal other than mouse is unpredictable.

While the level of skill of an artisan practicing the claimed invention will be high, in view of the unpredictability of the state of the art, an artisan would require specific guidance from the disclosure to carry out the full breadth of the claimed invention.

The instant specification broadly teaches a genetically borderline hypertensive mouse, its lineage, and the use of said mice to produce the BPH/5 mouse (page 5, lines 2-20). The instant specification also broadly teaches the possible use of said mouse to "screen and evaluate various potential therapies or other modalities for their effectiveness in treating or alleviating preeclampsia, and evaluate any potential prophylactics." (page 5, lines 21-24) The instant specification further teaches a working example wherein strain matched breeding was carried out with either BPH/5 or wild-type C57Bl/6 mice and pregnancy outcomes were analyzed. (pages 13-26, Example 1, Figures 1-6) It is emphasized that while the art of record (eg. Makino et al., 1999 or Takimoto et al., 1996) teaches making a mouse or rat model of preeclampsia by treating the mouse or rat with a nitric oxide synthase inhibitor, no preeclampsia model produced by administration of the compounds to any other animal are taught. The specification does not teach whether any other animal model could be produced. Because of the differences in physical structure, reproductive systems, metabolic systems, as well as genomes, between the species encompassed in the genus, any animal, from a mouse or rat, specific guidance would be required to make a preeclampsia animal model of any species other than mouse or rat by the method of administering said compounds.

Furthermore, the art and the instant specification do not teach administration of a compound to a pregnant BPH/5 mouse, wherein symptoms of preeclampsia are ameliorated or treated, wherein said compound is known to be useful in the amelioration or treatment of preeclampsia, therefore, the art of record nor the instant specification does not teach that the BPH/5 mouse is a recognized model of preeclampsia. Further, the instant specification does not teach a BPH/5 model of preeclampsia which could be used in a method for screening for compounds useful for the treatment of preeclampsia, wherein said animal is any animal other than mouse. In order for a skilled artisan to be enabled for the full scope of the claimed invention, the specific guidance provided by the art and the instant specification for a method for screening for compounds useful for the treatment or amelioration of preeclampsia using BPH/5 mouse model of preeclampsia would have to be sufficient to enable a skilled artisan to make and use said model of preeclampsia with any animal other than mouse. However, in view of the unpredictability of the art of transgenesis in order to make any BPH/5 animal other than mouse a model for preeclampsia and the lack of specific guidance to use a BPH/5 mouse, any BPH/5 animal, or any mouse or animal having a BPH/5 phenotype in a method for screening for compounds useful for the treatment or amelioration of preeclampsia, it would take an extensive amount of experimentation by a skilled artisan to make and use any BPH/5 animal other than mouse in a method for screening for compounds useful for the treatment or amelioration of preeclampsia. Further, wherein the screening for compounds useful for the treatment or amelioration of preeclampia in a mouse is taught in the art, it is not sufficient guidance for the screening for compounds

useful for the treatment or amelioration of preeclampsia in any animal other than mouse. For example, methods of administration, dosages, and even compounds utilized in a mouse model is not necessarily predictive in any animal model other than mouse. Further, a compound that eliminates the symptoms of preeclampsia in a mouse may not necessarily eliminate the symptoms of preeclampsia in a human. In view of the breadth of the claimed invention encompassing any animal and the lack of guidance from the art to make a BPH/5 model in any animal other than a murine animal, the specific guidance provided by the instant specification to use a BPH/5 mouse with induced preeclampsia does not enable a skilled artisan to modify the method of the claimed invention to make a BPH/5 model of preeclampsia comprising any animal other than murine. In order for the full breadth of the claimed invention to be enabled, a skilled artisan would have to be provided sufficient specific guidance to induce preeclampsia in any BPH/5 model comprising any animal other than murine. Lacking any disclosed specific guidance in the art or the instant specification to make and use a preeclampsia model comprising a BPH/5 animal other than murine, it would take an undue burden of necessary experimentation for a skilled artisan to make or use the claimed invention.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the claimed invention is not enabled for its full breadth and limiting the scope of the claimed invention to a method for screening for compounds useful for the treatment or amelioration of preeclampsia and/or symptoms thereof comprising inducing preeclampsia in a BPH/5 murine.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 13, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Makino et al. (Eur J Pharm 371:159-167, 1999).

The claims are drawn to a method for screening for compounds useful for the treatment or amelioration of preeclampsia and/or the symptoms thereof comprising inducing preeclampsia in an animal with a BPH/5 phenotype, administering a test compound to the animal; and monitoring the animal for amelioration or elimination of preeclampsia or its symptoms, wherein said method further comprises comparing the induced preeclampsia condition in said animal with the induced preeclampsia condition in a control animal that did not receive said candidate compound.

Makino et al. teach a method of using a preeclampsia rat model to screen the effect of adrenomedullin. Preeclampsia was induced in pregnant rats by administration of the NO synthase inhibitor, N-nitro-L-arginine methyl ester (L-NAME), which increased

basal systolic blood pressure in pregnant and non-pregnant rats. Pregnant rats receiving L-NAME also showed a higher fetal mortality than did intact rats, and showed "preeclampsia-like symptoms consisting of hypertension, intrauterine growth restriction, proteinuria and renal glomerulus injury." (page 164, paragraph 3) Pregnant and non-pregnant rats were administered adrenomedullin, a peptide thought to play a role in the adaptation of the vascular system during pregnancy and in the regulation of the placental vascular tone and is therefore be considered a candidate compound for alleviating the symptoms of preeclampsia. Authors teach that blood pressure was measured in pregnant L-NAME-treated animals either receiving or not receiving adrenomedullin and found "infusion of adrenomedullin reversed hypertension and decreased the pup mortality induced by L-NAME in animals in late gestation, but not in animals in early gestation and in non-pregnant rats." (page 165, paragraph 2) While Makino et al. does not teach the BPH/5 mouse, the rat model of preeclampsia taught by Makino et al. exhibited hypertension, proteinuria, renal glomerulus injury, endothelial dysfunction, and a higher fetal mortality rate, indicating that said rat model has the same defining characteristics as the claimed BPH/5 mouse of the instant application (page 5, lines 15-20 and page 9, lines 21-24 of instant specification). Therefore, the teachings of Makino et al. encompasses the limitations of the claim such that the art anticipates the invention of Claim 1. The claim is therefore rejected as being anticipated by prior art.

8. Claims 1-5 and 13-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Takimoto et al. (Science 274(5289): 995-998, 1996).

The claims are drawn to a method for screening for compounds useful for the treatment or amelioration of preeclampsia and/or the symptoms thereof comprising inducing preeclampsia in an animal with a BPH/5 phenotype, administering a test compound to the animal; and monitoring the animal for amelioration or elimination of preeclampsia or its symptoms, wherein said method further comprises comparing the induced preeclampsia condition in said animal with the induced preeclampsia condition in a control animal that did not receive said candidate compound, wherein said animal is a mouse, and wherein said animal is a BPH/5 mouse.

Takimoto et al. teach a method for screening for compounds useful for preeclampsia comprising transgenic female mice carrying the human angiotensinogen gene bred with transgenic male mice carrying the human renin gene. The authors teach that said transgenic female mice developed hypertension at 19 days of gestation and showed morphological abnormalities such as enlarged glomeruli and proteinuria, which is consistent with a preeclampsia-like phenotype. The authors measured blood pressure throughout pregnancy and found that said female mice began to show hypertension at 14 days of gestation and blood pressure continued to rise until the day before delivery and returned to non-pregnant levels 3 days post delivery. Further, the authors teach administration of said female mice with ES-8891, an inhibitor specific for human renin, which in humans originates from the placenta and has been shown to rise during pregnancy and could therefore be used for the treatment of preeclampsia. The authors teach that treatment of said female mice with ES-8891 at 17 days of gestation significantly reduced blood pressure, while ES-8891 at 17 days of gestation had no

effect on wild-type mice. Preeclampsia mice not treated with ES-8891 showed phenotypes such as a 38% survival rate with 15% having generalized seizures, 25% having convulsions and all having delayed delivery, that was not seen in non-hypertensive mice. While Takimoto et al. does not teach the BPH/5 mouse, the rat model of preeclampsia taught by Takimoto et al. exhibited hypertension, proteinuria, renal glomerulus injury, endothelial dysfunction, and a higher fetal mortality rate, indicating that said rat model has the same defining characteristics as the claimed BPH/5 mouse of the instant application (page 5, lines 15-20 and page 9, lines 21-24 of instant specification). Therefore, the teachings of Takimoto et al. encompasses the limitations of the claim such that the art anticipates the invention of claims 1-5 and 17-211. The claim is therefore rejected as being anticipated by prior art.

Conclusion

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Norma C Alonzo whose telephone number is 571-272-2910. The examiner can normally be reached on 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NCA

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